EXAMPLE 8

Antitumor activity of [2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl) adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester (nucleotide conjugate) and 2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine (nucleoside) in a human breast carcinoma xenograft model (MDA-MB-231) in vivo.

The antitumor activity of nucleotide conjugate and its corresponding nucleoside has been compared in the human breast carcinoma xenograft MDA-MB-231 model in nude mice.

Tumor bearing mice were randomized on day 21 after MDA-MB-231 tumor cell inoculation and were distributed to treatment groups of 9 animals per group. Treatment was started on day 21. At this time point the animals had well vascularized tumors of about 400 mg. The animals were treated orally once daily for 2 weeks with nucleotide conjugate and its corresponding nucleoside on days 21-25 and 28-32. Doses ranged from 6.25 % to 50 % of the Maximum Tolerable Doses (MTD's). Control animals were treated with the solvent (vehicle) only. Median tumor volumes on day 49 are shown in Table 1.

Compound	MTD	Dose (mg/kg/injection)	Tumor volume (mm^3)	Tumor inhibition (%)
Control	-	0	3430	
Nucleoside*	6.25 %	2.5	1862	46
Nucleoside*	12.50 %	5.0	550	84
Nucleoside*	25.00 %	10.0	172	95
Nucleoside*	50.00 %	20.0	108	97
Nucleotide coniugate**	6.25 %	12.5	1267	63
Nucleotide coniugate**	12.50 %	25.0	196	94
Nucleotide coniugate**	25.00 %	50.0	108	97
Nucleotide coniugate**	50.00 %	100.0	51	99

*2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine

**[2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester

The antitumor efficacy of the nucleotide was significantly ($p < 0.05$) higher than that of the corresponding nucleoside at all doses

Example 9

Antitumor activity of [2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl) adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester (nucleotide conjugate) and 2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine (nucleoside) in a human prostate carcinoma xenograft model (PC-3) in vivo

The antitumor activity of nucleoside conjugate and nucleoside has been compared in the human prostate carcinoma xenograft PC-3 model in nude mice.

Tumor bearing mice were randomized on day 7 after PC-3 tumor cell inoculation and were distributed to treatment groups of n = 10 animals per group. Treatment was started on day 7. The animals were treated intraperitoneally (ip) once daily for 5 consecutive days with nucleotide conjugate or nucleoside. Dosages included 100 and 50 % of the Maximum Tolerable Doses (MTD's). Control animals were treated with the corresponding solvent (vehicle) only. On day 52, the primary tumors were explanted and the tumor weights were determined. The median tumor weights are shown in Table 1.

Compound	MTD	Dose (mg/kg/injection)	Tumor weight (mg)	Tumor inhibition (%)
Control (Vehicle)	-	0	506	
Nucleoside*	50 %	20	303	40
Nucleoside*	100 %	40	202	60
Nucleotide coniugate**	50 %	50	92	82
Nucleotide coniugate**	100 %	100	64	87

*2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine

**[2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester

The antitumor efficacy of nucleoside conjugate was significantly higher ($p < 0.01$) than that of nucleoside at both doses.

Example 10

Antitumor activity of [2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester (nucleotide conjugate) and 2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine (nucleoside) in a human ovarian carcinoma xenograft model (SKOV-3) in vivo

The antitumor activity of nucleotide conjugate and nucleoside has been compared in the human ovarian carcinoma xenograft SKOV-3 model in nude mice.

Tumor bearing mice were randomized on day 6 after SKOV-3 tumor cell inoculation and were distributed to treatment groups of 9 animals per group. Treatment was started on day 6. The animals were treated intraperitoneally (ip) once daily on days 6-10 and 13-17 with nucleotide conjugate or nucleoside. Dosages ranged between 6.25 and 100 % of the Maximum Tolerable Doses (MTD's). Control animals were treated with solvent (vehicle) only. Median tumor volume at the end of the treatment period (day 17) is shown In Table 1.

Compound	MTD	Dose (mg/kg/injection)	Tumor volume (mm^3)	Tumor inhibition (%)
Control	-	0	256	
Nucleoside*	25 %	7.5	162	37
Nucleoside*	50 %	15.0	108	58
Nucleoside*	100 %	30.0	126	51
Nucleotide coniugate**	25 %	18.8	144	44
Nucleotide coniugate**	50 %	37.5	108	58
Nucleotide conjugate**	100 %	75.0	63	75

*2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine

**[2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester

The antitumor efficacy of the nucleotide conjugate was significantly higher ($p < 0.01$) than that of the nucleoside at MTD.

Example 11

Antitumor activity of [2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester (nucleotide conjugate) and 2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine (nucleoside) in a human pancreatic carcinoma xenograft model (AspC1) in vivo

The antitumor activity of nucleotide conjugate and nucleoside has been compared in the human pancreatic carcinoma xenograft AspC1 model in nude mice.

Tumor bearing mice were randomized on day 6 after AspC1 tumor cell inoculation and were distributed to treatment groups of 10 animals per group. Treatment was started on day 6. The animals were treated intraperitoneally (ip) once daily on days 6-10 and 20-23 with nucleotide conjugate or nucleoside. Dosages included 100 and 50 % of the Maximum Tolerable Doses (MTD's). Control animals were treated with solvent (vehicle) only. Median tumor weight at the end of the experiment (day 30) is shown In Table 1.

Compound	MTD	Dose (mg/kg/injection)	Tumor weight (mg)	Tumor inhibition (%)
Control (Vehicle)	-	0	230	-
Nucleoside*	50 %	15.0	160	30
Nucleoside*	100 %	30.0	150	35
Nucleotide coniugate**	50 %	37.5	80	65
Nucleotide conjugate**	100 %	75.0	10	96

*2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine

**[2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester

The antitumor efficacy of nucleotide conjugate was significantly higher ($p < 0.01$) than that of Nucleoside at both doses.

Example 12

Antitumor activity of [2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl) adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester (nucleotide conjugate) and 2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine (nucleoside) in a human cervix carcinoma xenograft model (KB-3-1) in vivo

The antitumor activity of nucleotide conjugate and nucleoside has been compared in the human cervix carcinoma xenograft KB-3-1 model in nude mice.

Tumor bearing mice were randomized on day 8 after KB-3-1 tumor cell inoculation and were distributed to treatment groups of 9 animals per group. Treatment was started on day 8. The animals were treated intraperitoneally (ip) once daily for 5 consecutive days (days 8-12) with nucleotide conjugate or nucleoside. Dosages included 100 and 50 % of the Maximum Tolerable Doses (MTD's). Control animals were injected with solvent (Vehicle). Median tumor weight on day 29 is shown in Table1.

Compound	MTD	Dose (mg/kg/injection)	Tumor volume (mm^3)	Tumor inhibition (%)
Control (Vehicle)	-	0	3313	-
Nucleoside*	50 %	20	1059	68
Nucleoside*	100 %	40	1705	49
Nucleotide coniugate**	50 %	50	877	74
Nucleotide conjugate**	100 %	100	104	97

*2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine

**[2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester

The antitumor efficacy of nucleotide conjugate was significantly higher ($p < 0.01$) than that of Nucleoside at the MTD.

Summary of anti-tumor activity of the nucleotide conjugate [2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl) adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester and the nucleoside 2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl) adenine

Compound	Dose (% MTD)	Tumor inhibition (%)					
		HCT-15	SKOV-3[a]	MDA-MB-231	PC-3	AspC1	KB-3-1
Nucleoside*	6.25			46			
Nucleoside*	12.50			84			
Nucleoside*	25.00		37	95			
Nucleoside*	50.00	25	58	97	40	30	68
Nucleoside*	100.00	42	51		60	35	49
Nucleotide coniugate**	6.25			63			
Nucleotide coniugate**	12.50			94			
Nucleotide coniugate**	25.00		44	97			
Nucleotide coniugate**	50.00	62	58	99	82	65	74
Nucleotide coniugate**	100.00	98	75		87	96	97

*2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine
**[2-Chloro-9-(2'-deoxy-2'-fluoro-β-D arabinofuranosyl)adenine] -5-phosphoric acid-(3-dodecylmercato-2-decyloxy) propyl ester

[a] Tumor inhibition at the end of the treatment period

Type of tumors:
HCT-15): human colon carcinoma xenograft
SKOV-3: ovarian carcinoma xenograft
MDA-MB-231: human breast carcinoma xenograft
PC-3: human prostate carcinoma xenograft
AspC1: human pancreatic carcinoma xenograft
KB-3-1: human cervix carcinoma xenograft

Tumor bearing mice were distributed to treatment groups of 9-10 animals per group.Treatment Treatment cycle(s)(one or two) were performed consisting of once daily intraperitoneal administrations for 5 consecutive days. Dosages were in the range of 6.25 % and 100 % of the Maximum Tolerated Doses (MTD's). Control animals were treated with solvent (vehicle) only, The percentage of tumor inhibition refers to the median tumor size of the vehicle treated control group and dose groups at the end of each experiment.

Conclusion

Superior activity of the nucleotide conjugate was found for:
HCT-15): human colon carcinoma xenograft
SKOV-3: ovarian carcinoma xenograft
MDA-MB-231: human breast carcinoma xenograft
PC-3: human prostate carcinoma xenograft
AspC1: human pancreatic carcinoma xenograft
KB-3-1: human cervix carcinoma xenograft